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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/826,745	04/04/2001	Christopher B. Darrow	G&C 142.3-US-UI	8855

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EXAMINER

WALLENHORST, MAUREEN

ART UNIT	PAPER NUMBER
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1743

DATE MAILED: 03/29/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/826,745

Applicant(s)

DARROW ET AL.

Examiner

Maureen M. Wallenhorst

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
 - If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
 - If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
 - Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☐ Responsive to communication(s) filed on ____.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-35 is/are pending in the application.
- 4a) Of the above claim(s) ____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) ____ is/are allowed.
- 6) ☒ Claim(s) 1-35 is/are rejected.
- 7) ☐ Claim(s) ____ is/are objected to.
- 8) ☐ Claim(s) ____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☒ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on ____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
 - ☐ Certified copies of the priority documents have been received in Application No. ____.
 - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- ☒ Notice of References Cited (PTO-892)
- ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date 11/7/01, 6/4/02, 12/18/02
- ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date. ____
- ☐ Notice of Informal Patent Application (PTO-152)
- ☐ Other: ____

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1. The disclosure is objected to because of the following informalities: On page 8, line 20 of the specification, the phrase “Fig. 24 depicts” should be changed to “Figs. 24a, 24b and 24c depict— since Figure 24 has a part a), b) and c).

Appropriate correction is required.

2. Claims 1-35 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 is indefinite since there is no positive step in the method of combining the fluorescent sensor molecules with the solution or sample containing a polyhydroxylate analyte. Therefore, it is not understood how the solution can have a total fluorescence to be determined in step a) of the method.

On line 2 of claim 4, the phrase “AFSA species” should be changed to “FS species— since claim 1 recites an AFS and a FS species of fluorescent sensor molecule.

In claim 13, it is not clear what “COB” stands for. See this same problem in claim 21.

In claim 14, it is not clear what “NIB” stands for. See this same problem in claim 22.

On lines 7-8 of claim 16, the abbreviation “(FS)” should be inserted after the phrase “the fluorescent sensor molecule not bound to the polyhydroxylate analyte” since this abbreviation is used later in the claim to refer to this species of sensor molecule. Step b) of claim 16 is redundant with step a) since step a) already recites contacting the sample with the fluorescent sensor molecules. Claim 16 is indefinite since it is not understood why the emission beam emanating from the sensor molecules is measured in step c) of the method when earlier in the claim, the fluorescent lifetimes of the different species of sensor molecules are described. It is

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not understood why the fluorescent lifetimes of the sensor molecules are not measured in step c) of the method.

In claims 17 and 18, the phrase “the relative fluorescent contribution” should be changed to –the relative fluorescent lifetime contribution—so as to use the same terminology as in claim 16.

In claims 19 and 20, the phrase “the total fluorescence” lacks antecedent basis.

Claims 29 and 30 are indefinite since these claims recite that the fluorescent lifetimes are calculated. However, claim 16 does not recite that fluorescent lifetimes of the sensor molecules are measured, only that an emission beam is detected.

3. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

4. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

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5. Claims 1, 4-6, 12, 16-20, 23 and 27-30 are rejected under 35 U.S.C. 102(e) as being anticipated by Lakowicz et al (US 2002/0045268).

Lakowicz et al teach of an optical method for measuring analytes with metal-ligand probes. The method comprises the steps of combining a sample containing an analyte such as glucose with a fluorescent metal-ligand complex probe. The probe exists in the sample in a bound form and an unbound form. When the probe is bound to the analyte, the naturally occurring fluorescent lifetime of the probe changes. Therefore, the fluorescent lifetime of the probe will be different depending upon whether it is bound to analyte or unbound. The method comprises exciting the sample/probe mixture with radiation from a source such as a pulsed laser, light emitting diode, etc. The fluorescent lifetimes of the bound and unbound forms of the probe are measured using the techniques of phase modulation fluorometry or time-resolved fluorometry. The analyte concentration is determined from the decay time of the fluorescent probe and its dependence on the analyte of interest. Lifetime-based sensing is preferred by Lakowicz et al over intensity-based methods because the lifetime is mostly independent of the probe concentration and is unaffected by photobleaching or washout of the probe.

See Figure 12 of Lakowicz et al where glucose is one of the analytes measured in the method, and paragraph nos. 37, 45-46, 53-56 and 63 in Lakowicz et al.

6. Claims 1-2, 9, 12, 16, 19-20, 25-27 and 31 are rejected under 35 U.S.C. 102(e) as being anticipated by Bell et al. (US Patent no. 6,366,793)

Bell et al teach of a method for measuring a polyhydroxylate analyte such as glucose contained in the interstitial fluid of a body. The method comprises the steps of providing a fluorescent sensor particle capable of generating an analyte signal in response to the analyte

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concentration in a body, placing the sensor particles in contact with the interstitial fluid of a body to generate a detectable signal, detecting the analyte signal and determining the concentration of the analyte contained in the interstitial fluid. The sensor particles reversibly bind to the analyte, and may contain dual diboronic acids conjugated to fluors. These sensor particles use photo-induced electron transfer between an amine group and the fluor as modulated by binding of glucose to the boronic acids. In the absence of glucose binding, the fluorescence of the fluorescent group is quenched. When the glucose is bound, the fluorescence is enhanced. The signal fluorescence is responsive to the binding of the glucose to the dual phenyl boronic acids. The signal fluorescence generates a first signal when it is contained in a bound state and a second signal when it is contained in an unbound state. The first and second signals are distinguishable in their optical properties. Both signals are responsive to the concentration of the analyte contained in the interstitial fluid since the relative distribution of bound and free sensor molecules is controlled by a chemical equilibrium governed by the analyte concentration. Measurements of the optical properties of the bound and unbound sensor molecules are mathematically combined to determine the analyte concentration. Bell et al teach that fluorescence lifetime can be the optical property of the bound and unbound sensor molecules that is measured in the method. See lines 60-67 in column 3, column 4 and lines 1-52 in column 5 of Bell et al.

7. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

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8. The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

9. Claims 1-35 are rejected under 35 U.S.C. 103(a) as being unpatentable over Satcher, Jr. et al (US Patent no. 6,682,938) in view of either Lakowicz et al or Bell et al.

For a teaching of Lakowicz et al and Bell et al, see previous paragraphs in this Office action.

Satcher, Jr. et al teach of a method for sensing glucose molecules in a sample by combining the sample with analyte sensing fluorescent molecules. The fluorescent molecules have excitation wavelengths greater than 400 nm, and specifically and reversibly bind to glucose. The fluorescent molecules have a substrate recognition component that binds to glucose (typically a substituted aryl boronic acid), a fluorescent switch that is mediated by a substrate recognition event, and a fluorophore. The sensor molecules are based on photoelectron transfer (PET). The sensor molecule is designed so that the photo-excited fluorophore and the boron atom compete for unbonded amine electrons. In the absence of glucose binding, electron transfer occurs with the fluorophore, causing fluorescent quenching and weak emission. When glucose is bound to the boronate group, the average charge on the boron atom becomes more positive which increases the attraction of the unbonded electrons, preventing electron transfer, thus disabling the fluorescent quenching, and therefore, causing a strong emission. The fluorescent

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sensor molecules can be transition metal-ligand boronate compounds or aryl boronic fluorescent molecules having the same formula as recited in instant claims 3 and 32 (see figure 1 of Satcher, Jr. et al). The fluorophore in the molecules can be a COB or a NIB fluorophore. See lines 27-28 in column 27 and example 3 in Satcher, Jr. et al. The pKa of the amine in the sensor molecules is between 2 and 7. The fluorescent sensor molecules are immobilized in a glucose permeable biocompatible polymer matrix to form an implantable sensor. Once in a body of interstitial fluid, the sensor is interrogated by applying excitation light through the skin and monitoring the intensity or fluorescence lifetime of the emitted fluorescence externally. The measured emitted light allows the quantification of glucose concentration. Satcher, Jr. et al fail to specifically teach that the fluorescence lifetime of both the bound and unbound fluorescent sensor molecules are measured to determine their relative contribution to the overall fluorescence of the sample analyzed, and of correlating the measured fluorescence lifetimes to the glucose concentration in the sample.

Based upon the combination of Satcher, Jr, et al and either Lakowicz et al or Bell et al, it would have been obvious to one of ordinary skill in the art at the time of the instant invention to measure the fluorescence lifetime of both the bound and unbound fluorescent sensor molecules in the method taught by Satcher, Jr. et al so as to determine their relative contribution to the overall fluorescence of the sample analyzed, and to correlate their measured fluorescence lifetimes to the glucose concentration in the sample since both Lakowicz et al and Bell et al teach that both signals of bound and unbound fluorescence lifetimes are responsive to the concentration of an analyte contained in a sample since the relative distribution of bound and

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free sensor molecules is controlled by a chemical equilibrium governed by the analyte concentration.

10. Claims 1-3, 9-12, 15-16, 19-20, 23-28 and 31-33 are rejected under 35 U.S.C. 103(a) as being unpatentable over Van Antwerp et al (US Patent no. 6,002,954) in view of either Lakowicz et al or Bell et al. For a teaching of Lakowicz et al and Bell et al, see previous paragraphs in this Office action.

Van Antwerp et al teach of the detection of polyhydroxylated compounds such as glucose using boronate-based chemical optical sensors. The sensors comprise a permeable membrane and a matrix that immobilizes chemical/optical sensor molecules. The sensor is implantable into the body of a person to be tested. The sensor molecules are boronate-based sugar binding compounds that reversibly bind to glucose to form both a bound form and an unbound form. Upon binding to glucose, the fluorescence of the sensor molecules changes due to intramolecular electron transfer. In one embodiment, the sensor molecules contain an arylboronic acid moiety attached to an amine-functionalized dye molecule. The sensor molecules can have the formula (I) depicted on line 35 in column 8 of Van Antwerp et al, which is the same formula as recited in instant claims 3 and 32. The method taught by Van Antwerp et al includes the steps of irradiating the implanted sensor with a light source such as a lamp, LED, or a pulsed or modulated laser diode. The light source illuminates the implanted sensor, and a detector detects the intensity of the emitted light, which is typically fluorescent. Van Antwerp et al teach that other modes of measurement may also be used such as absorbance, reflectance and fluorescence lifetimes. The detected fluorescent light or fluorescent lifetimes are then used to quantify the amount of glucose in the individual being tested with the sensor. See lines 30-40 in column 7,

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column 8 and lines 4-25 in column 16 of Van Antwerp et al. Van Antwerp et al fail to specifically teach that the fluorescence lifetime of both the bound and unbound fluorescent sensor molecules are measured to determine their relative contribution to the overall fluorescence of the sample analyzed, and of correlating the measured fluorescence lifetimes to the glucose concentration in the sample.

Based upon the combination of Van Antwerp et al and either Lakowicz et al or Bell et al, it would have been obvious to one of ordinary skill in the art at the time of the instant invention to measure the fluorescence lifetime of both the bound and unbound fluorescent sensor molecules in the method taught by Van Antwerp et al so as to determine their relative contribution to the overall fluorescence of the sample analyzed, and to correlate their measured fluorescence lifetimes to the glucose concentration in the sample since both Lakowicz et al and Bell et al teach that both signals of bound and unbound fluorescence lifetimes are responsive to the concentration of an analyte contained in a sample since the relative distribution of bound and free sensor molecules is controlled by a chemical equilibrium governed by the analyte concentration.

11. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

Please make note of: Satcher, Jr. et al (US Patent no. 6,673,625) who teach of saccharide-sensing molecules having enhanced fluorescent properties.

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12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maureen M. Wallenhorst whose telephone number is 571-272-1266. The examiner can normally be reached on Monday-Wednesday from 6:30 AM to 4:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jill Warden, can be reached on 571-272-1267. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Maureen M. Wallenhorst
Primary Examiner
Art Unit 1743

mmw

March 22, 2004

Maureen M. Wallenhorst
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